Chapter 2
Equipment Overview

2.1 The “Build-It-Yourself (BIY)” Approach

Due to the still relatively high costs of dedicated commercial flow instrumentation, the majority of chemists around the world practice the “build-it-yourself” (BIY) or also “do-it-yourself” (DIY) approach. Ever since the few early reports on flow synthesis [1, 2], the most preferred option in the community to date is to assemble continuous flow devices for synthetic purposes using redundant parts from HPLC and GC instrumentation. However, this approach is often associated with major reproducibility issues. Indeed, the published flow procedures from the last decade have been only very rarely reproduced and further employed beyond the original reports. For this reason, the research performed in such devices remains beyond the scope of this book.

2.2 Dedicated Continuous Flow Systems for Organic Synthesis

With growing interest in continuous flow synthesis on laboratory scale, the demand for sophisticated instrumentation has also increased in recent years. With the market introduction of the modular AFRICA™ system by Syrris, the H-Cube™ flow hydrogenator by ThalesNano, the Ehrfeld module platform for flow, the CPC-College system, and few other platforms between 2005 and 2006, automated continuous flow synthesis became available for laboratory-scale synthesis. Safe and reproducible work is now possible without any “engineering” efforts for “BIY” flow systems. The major players on the market for laboratory continuous flow equipment with the various instrumental equipments are summarized below.
2.2.1 ThalesNano Nanotechnology Inc. [3, 4]

2.2.1.1 H-Cube™

The H-Cube™ was introduced as a stand-alone flow hydrogenation reactor back in 2005. The bench-top, shoebox-sized system easily fits into any laboratory fume hood and allows straightforward access to hydrogen-involving reactions under flow conditions. Eliminating the need of a specially equipped hydrogenation room and handling of pressurized hydrogen gas bottles, the instrument allows fast, safe, and cost-efficient processing by on-demand hydrogen generation through water electrolysis.

A piston pump delivers the substrate–solvent mixture into the system where it is mixed with the generated hydrogen gas, before passing over a cartridge packed with a heterogeneous catalyst. The reaction mixture can be heated up to 100 °C and pressurized up to 100 bar. The instrument can be run in three different modes—“no hydrogen mode,” “full mode,” and “controlled mode.” The “no hydrogen” mode allows the use of the instrument for different chemistries besides hydrogenation. In “full mode,” all the generated hydrogen is mixed with the reaction mixture at atmospheric pressure, while the “controlled mode” allows pressurizing the system with selected amount of hydrogen up to 100 bar. The flow rate of the reaction mixture can be selected in the range 0.5–3 mL/min via the touchscreen and is communicated to the external pump. The reaction takes place in the heated cartridge holder. The cartridge concept (CatCart®) allows the use of various commercial solid catalysts as well as newly developed ones. Three different sizes of stainless steel CatCarts® are available —30, 50, and 70 mm in length. The use of CatCarts® eliminates the need of catalyst removal after the reaction has finished. With the H-Cube™ hydrogenator, amounts in the range of several milligrams up to 10 g can be processed successfully.

2.2.1.2 H-Cube Pro™

The H-Cube Pro™ (Fig. 2.1) is a newer generation of the H-Cube family, integrating the features of previous systems [6–9] while giving the opportunity to widen the reaction scope that can be explored under flow conditions. New features include:

- Two hydrogen cells to generate up to 60 mL/min hydrogen
- Reaction temperatures in the range of 10–150 °C
- Support of external modules—gas module for the controlled supply of gases other than hydrogen, Phoenix Flow Reactor (see below), etc.
- Full automation and external software control
2.2.1.3 H-Cube Midi™

The H-Cube Midi™ is developed as scale-up version of the H-Cube concept. In this manner, this flow hydrogenator is able to deliver an increased productivity of up to 500 g/day of product. The reaction mixture can be flowed through the system with an automatically controlled piston pump at flow rates of 3–25 mL/min. The working reaction temperature can be up to 150 °C, and CatCarts® of 9.5 × 90 mm in size are used, able to carry several grams of catalyst.

2.2.1.4 H-Cube Mini™

The H-Cube Mini™ (Fig. 2.1) is developed for education purposes in academia and represents a simplified version of the H-Cube instrument.

2.2.1.5 Phoenix Flow Reactor™

The Phoenix Flow Reactor™ (Fig. 2.1) is a high-temperature reactor for heterogeneous or homogenous reaction in flow conditions. It combines the properties of two earlier instruments—the X-Flash and the X-Cube [5–7]. It can work as an add-on
for the H-Cube and H-Cube Pro reactors or as a stand-alone instrument. The reactor works with capillary tubing (coils) from stainless steel, Hastelloy®, or Teflon®. Respectively, reaction temperatures in the range of 150–450 °C are accessible. The standard 30 and 70 mm CatCarts® can be used in temperature regimes up to 250 °C. Specially developed 125 and 250 mm CatCarts® allow working conditions of up to 450 °C (petrochemical applications).

2.2.1.6 IceCube™ Flow Reactor

The IceCube Flow Reactor™ (Fig. 2.2) is designed to cover the temperature range of −70–80 °C. It is a software-controlled, modular system containing an ozone-generating module, a reactor module, and a pump module. It enables the performance of highly energetic reactions such as ozonolysis, azidation, nitration, or lithiation in a safe manner. The ozone generator (ozone module) is able to deliver 14 % (v/v) of ozone at 20 mL/min oxygen flow rate. The applicable oxygen flow rate is 10–100 mL/min.

The reactor module possesses two reaction plates, equipped with Peltier cooling/heating modules for precise temperature control and a Teflon reaction line. The use of an in-line quench effectively prevents the isolation of dangerous intermediates.

![Fig. 2.2 ThalesNano instruments—(a) IceCube reactor; (b) ozone module; (c) pump module](image-url)
2.2.2 Syrris [8]

2.2.2.1 ASIA Modular System™

The ASIA modular system (Fig. 2.3) allows a wide range of configuration options to meet the synthetic requirements of various chemical processes. The flow system can be controlled either “manually” or interfaced to a computer. The specifications of the system include the following:

- Temperature regimes: $-15$ to $+250$ $^\circ$C
- Liquid phase reactor volumes: 62.5 $\mu$L, 250 $\mu$L, 1 mL, 4 mL, and 16 mL
- Solid phase reactor volumes: 0.7, 2.4, 5.6, and 12 mL
- Working pressures: 0–20 bar
- Flow rates: 1 $\mu$L/min–10 mL/min using continuous syringe pumps
- Wetted materials: glass, Teflon®, PCTFE, stainless steel, and Hastelloy®

The system allows the implementation of tube (coil), chip, and glass column reactors as well as the realization of multistep syntheses, where the reactors can be combined and used sequentially. An interesting module is the FLLEX™ liquid–liquid extractor, allowing an in-line extraction as integrated purification step.

2.2.2.2 AFRICA Modular System™

The AFRICA system is a highly sophisticated, fully automated, modular flow system for R&D chemists enabling the production of kilogram quantities of product overnight [9].
2.2.3 Vapourtec Ltd [10]

2.2.3.1 R-Series Modular System

The R-Series modular system (Fig. 2.4) consists of two main modules with different reactor options—tube (coil), column, tube in tube, etc. The R-series pump module (R1 or R2 in various configurations) allows working with flow rates of 0.05–50 mL/min and 10–200 bar pressure. An acid-resistant modification of the pump is also available which allows the use of concentrated sulfuric and fuming nitric acid. The R-series reactor module (R4 module) provides four independently temperature-controlled reactor positions for using exchangeable reactors:

- Standard PFA coiled tube reactor: 2, 5, and 10 mL reactor volumes
- Stainless steel 316 or Hastelloy coiled tube reactor: 2, 5, and 10 mL reactor volumes; usable for reactions up to 250 °C
- Cooled coil reactor: for reactions at −70 °C to ambient
- Glass column reactor: −40 to 150 °C temperature regimes covered; for solid reagents/catalysts/scavengers

The fully automated version features software control, fraction collector, additional pump line, and an autosampler.

2.2.3.2 E-Series Modular System

The E-series modular system (Fig. 2.4) is a newer development from Vapourtec. It is available in four basic configurations—easy scholar, easy polymer, easy medchem, and easy photochem. All of the configurations have three V3 model

![Fig. 2.4 Vapourtec Instruments—(a) R-series; (b) E-series](image)
pumps, able to handle light suspensions and even slurries. The four flow systems support up to two reactor positions which can accommodate the full range of reactors available as separate modules from Vapourtec. The easy photochem system is intended for photochemical syntheses and can be equipped with either a LED light source (365–500 nm) or with a high-intensity, medium-pressure Hg lamp combined with a plethora of optical filters for isolated irradiation wavelengths. Additional chemistry tools are integrated into the software package of all models.

2.2.4 Uniqsis Ltd [11]

2.2.4.1 FlowSyn™

The FlowSyn is a compact flow system (Fig. 2.5) with two integrated high-pressure pumps (up to 20 mL/min flow rate, up to 200 bar pressure) and two independent heated reactor modules—for column or chip reactors (up to 150 °C) and a coil reactor heater (up to 260 °C). Combining a chip reactor as a mixing device with a coil reactor is possible. The coil reactors are available in various materials—stainless steel, Hastelloy, copper, PTFE, and PFA. Glass columns and static mixers/reactor chips are also available on demand. On a modular basis, different add-on devices can be used—a fraction collector (Multi-X), liquid handler (Auto-LF), additional pump (Binary Pumping Module), or heater/chiller module (−88 °C Polar Bear™; −40 to 150 °C, Polar Bear Plus™)—and a higher throughput version (up to 100 mL/min; Maxi) etc.

2.2.4.2 FlowStart™

The FlowStart™ system is a modular entry level system (Fig. 2.5). It is a combination of two high-pressure pumps and a HotCoil™ reactor station, both controlled by the FlowStart™ software via LAN. The flow rate can be adjusted between 0.01–20 mL/min at pressures of up to 100 bar. Working temperatures of up to 260 °C can be achieved. The HotColumn™ is an optional module for up to six column reactors. Additional accessories include various back pressure regulators (5–50 bar), coil reactors (2–60 mL), etc.
2.2.5 Future Chemistry Holding BV [12]

2.2.5.1 Flow Start Evo

The Flow Start Evo is a compact, stand-alone flow system with various add-on modules (Fig. 2.6). The main module incorporates three syringe pumps (1 μL to 2.9 mL/min) and a microreactor (chip, internal volume ca. 100 μL) holder/heater (up to 140 °C). A photochemistry module as add-on allows irradiation at 250, 295, 365, and 470 nm. The high-temperature module allows working at temperatures between −10 and 200 °C. An additional back pressure regulator can keep an inside
system pressure of up to 5 bar. The optional combination with a gas module makes gas/liquid reactions easy and precisely handled. The application of many standard noncorrosive gases is possible. Finally, a computer control of the overall system is also possible.

2.2.5.2 Flow Start Expert

The Flow Start Expert (Fig. 2.6) is an advanced flow setup with fully automated liquid handling and integrated vacuum pump. The integrated automated valves, reagent vials, and sample collectors allow library synthesis. Inert conditions can be realized for sensitive chemistries. The system can be employed for radiopharmaceutical synthesis.

2.2.6 Chemtrix BV [13]

2.2.6.1 Labtrix® Start

The Labtrix® Start is another compact, plug-and-play platform for laboratory flow synthesis using microreactors (Fig. 2.7). The system compromises a combination of two syringe pumps (extendable up to five), microreactor holder/heater, and a temperature controller. The process window of the system ranges form −20 to 195 °C and 0–25 bar pressure. Various chip mixers/microreactors are available. Three different versions can be chosen—standard, flex, and ultraflex. The standard version allows working with basic conditions: the flex, with slightly acidic
conditions, and the ultraflex, with 70% nitric acid or 98% sulfuric acid in −20 to 75 °C range. Upgrades include a flow calculation tool, a catalyst reactor set, a pressure meter set, and an additional feed line.

2.2.6.2 Labtrix® S1

The Labtrix® S1 is a fully automated, plug-and-play platform for laboratory flow synthesis. It has five syringe pumps (1–2.5 mL), two of which can be connected for continuous delivery (Fig. 2.7). Automated sample collection holds up to 30 vials that can be addressed by a selection valve. The temperature/pressure ranges are the same as for the Labtrix® Start system. Three different versions can be obtained here as well—standard, flex, and ultraflex.

2.2.6.3 Kiloflow® and Plantrix®

The Kiloflow® and Plantrix® are glass and ceramic/silicon carbide modular reactors intended for scale-up flow synthesis on kilogram/t scale (Fig. 2.7).
2.2.7  Advion Inc. [14]

2.2.7.1  NanoTek®

The NanoTek® is a modular microfluidic system developed for radiochemical synthesis of PET and SPECT imaging probes (Fig. 2.8). The system can handle pressure of up to 28 bar and works in the temperature range of −40 to 220 °C. It consists of syringe pumps, a reactor module, and a concentrator/evaporator unit. The system can be extended to allow automated HPLC purifications of the obtained products. Various reactor volumes are available.

2.2.8  YMC Co. Ltd [15]

2.2.8.1  The KeyChem Reactors

The KeyChem concept includes two modular microreactor systems for laboratory flow applications—the KeyChem Basic and the KeyChem-L. Both systems are based on the use of syringe pumps in combination with reactor modules (Peltier thermostated) and either manual or computer control. Additionally, the KeyChem Lumino is available. It comprises a micromixer, a thermostat, and a UV LED light source for continuous flow photochemistry experimentation.

2.2.8.2  CYTOS-200 and CYTOS-2000

The CYTOS reactors are aimed at scaling-up synthesis and use of either syringe or piston pumps.
2.2.9 AM Technology [16]

2.2.9.1 Coflore® ACR and ATR

The Coflore® systems contain multistage flow reactors that are intended to overcome the problems of slurry and suspension processing under flow conditions while, at the same time, assuring efficient mixing. The patented mixing technique is based on freely moving agitators within each reactor section promoting efficient mixing by lateral shaking of the reactor body. This special action prevents phase separation. The Coflore® ACR system has a small footprint (Fig. 2.9) and fits on a standard laboratory bench [17]. It consists of two parts—the agitator and the exchangeable reactor block. Based on the reactor block, three different versions are available—ACR-20 (10–17 mL reactor volume), ACR-100 (30–90 mL), and ACR-X (countercurrent flow; for reactions or extractions). All of the configurations are designed to withstand temperatures of −40 °C up to 140 °C and ambient up to 10 bar pressure. The reactor block is available in stainless steel, Hastelloy®, or Teflon® versions.

The Coflore® ATR is an industrial flow reactor system with a capacity range of 0.1–10 L and is based on a tubular design. It can safely manage pressures up to 100 bar and temperatures from −90 °C up to 300 °C (stainless steel or Hastelloy®).

Fig. 2.9 Coflore ACR system from AM Technology
2.2.10  **Ehrfeld [18]**

2.2.10.1  **MMRS®**

The Modular MikroReaktionsSystem (MMRS) is a highly flexible concept providing more than 60 single modules for assembling a flow process on a laboratory scale [19]. The different modules are mounted together on a metal plate with a variable size. Multistep syntheses are also realizable. Using different sensors and actuators, real-time data useful for the process optimization can be collected easily. The specifications of the system include the following:

- Temperature regimes: $-25 \degree C$ to $200 \degree C$ ($-160 \degree C$ to $600 \degree C$)
- Working pressures: up to 100 bar
- Flow rates: 0.16–500 mL/min
- Wetted materials: Teflon®, FFKM, stainless steel, and Hastelloy®
- Modules for mixing, emulsifying, heterogeneous/homogeneous synthesizing, photochemistry

The system requires external pumps.

2.2.10.2  **FlowPlate®, ART®, and Miprowa®**

The reactors are intended for scale-up purposes on industrial level.

2.2.11  **Corning [20]**

The Corning flow reactors have a modular chip-based design and are aimed predominantly at large-scale and industrial-scale synthesis. In addition, the low-flow and the G1 systems offer possibilities for smaller-scale syntheses. A version of the G1 reactor was developed to allow photochemical synthesis using UV LED irradiation at 365 and 405 nm. The G3 and G4 are large-scale devices.

2.2.12  **Accendo Corporation [21]**

2.2.12.1  **Conjure™ Flow Chemistry**

The Conjure is a fully automated system for continuous synthesis. For library synthesis or screenings, up to 40 different materials can be preloaded. Automated segment preparation allows a broad spectrum of stoichiometries to be tested. The Conjure can be coupled easily with an LC/MS—automated sample preparation, dilution, and injections are possible. Multistep synthesis is also possible. Temperature regimes cover the range of $-20 \degree C$ to $100 \degree C$ [22].
2.2.12.2 Propel™ Flow Chemistry

The Propel is a modular system for flow synthesis specifically designed as a shared resource. The system can hold up to three reactant materials for screening, optimization, and the scale-up of a reaction. The programming interface allows an initial setup of up to nine experiments for optimizing stoichiometry, residence time, and temperature. The Propel system can routinely perform experiments with as little as 20 μL of precious reactants. A scale up to over 100 g is easily achievable. An on-line LC–MS module can be used as an extension.

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